ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OZURDEX 700 micrograms intravitreal implant in applicator

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One implant contains 700 micrograms of dexamethasone.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravitreal implant in applicator.
Disposable injection device, containing a rod-shaped implant. which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OZURDEX is indicated for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) (see section 5.1).

4.2 Posology and method of administration

OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Posology
The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4).

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's opinion may benefit from retreatment without being exposed to significant risk (see section 5.1).

Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated.

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4).

Special populations
Elderly (≥65 years old)
No dose adjustment is required for elderly patients.

Renal impairment
OZURDEX has not been studied in patients with renal impairment however no special considerations are needed in this population.

Hepatic impairment
OZURDEX has not been studied in patients with hepatic impairment, however no special considerations are needed in this population.

Paediatric population
There is no relevant use of OZURDEX in the paediatric population in macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).

Method of administration
Single-use intravitreal implant in applicator for intravitreal use only.
Each applicator can only be used for the treatment of a single eye.

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent).

A broad spectrum topical antimicrobial should be given prior to and on the day of the injection procedure. Adequate local anaesthesia should be administered. Remove the foil pouch from the carton and examine for damage (see section 6.6). Then, in a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Once the foil pouch is opened the applicator should be used immediately.

Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualisation is possible in the large majority of cases. In cases in which the implant cannot be visualised, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view.

Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial.

4.3 Contraindications

OZURDEX is contraindicated in

- Hypersensitivity to the active substance or to any of the excipients.
- Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- Advanced glaucoma which cannot be adequately controlled by medicinal products alone.

4.4 Special warnings and precautions for use

Monitoring
Any intravitreous injection can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always be used. In addition, patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection.

Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

Adverse reactions
Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections.

In clinical studies, cataract was reported more frequently in patients with phakic lens receiving a second injection (see section 4.8) with only 1 patient out of 368 requiring cataract surgery during the first treatment and 3 patients out of 302 during the second treatment.
As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. Of the patients experiencing an increase of IOP of ≥10 mmHg from baseline, the greatest proportion showed this IOP increase at around 60 days following an injection. Patients of less than 45 years of age are more likely to experience increases in IOP. Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post-injection as needed.

Other warnings and precautions
Corticosteroids should be used cautiously in patients with a history of *ocular herpes simplex* and not be used in active *ocular herpes simplex*.

The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended.

OZURDEX has not been studied in aphakic patients Therefore OZURDEX should be used with caution in these patients.

OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischemia. Therefore OZURDEX is not recommended.

Anti-coagulant therapy was used in 1.7% of patients receiving OZURDEX; there were no reports of hemorrhagic adverse events in these patients. Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40% of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with OZURDEX (27%) compared with the control group (20%). The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24%). OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Systemic absorption is minimal and no interactions are anticipated.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown teratogenic effects following topical ophthalmic administration (see section 5.3). There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. Long-term systemic treatment with glucocorticoids during pregnancy increases the risk for intra-uterine growth retardation and adrenal insufficiency of the newborn child. Therefore, although the systemic exposure of dexamethasone would be expected to be very low after local, intraocular treatment, OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast feeding

Dexamethasone is excreted in breast milk No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive and use machines

Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection (see section 4.8). They should not drive or use machines until this has resolved.

4.8 Undesirable effects

a) The clinical safety of OZURDEX has been assessed in two Phase III randomised, double-masked, sham-controlled studies in patients with macular oedema following central retinal vein occlusion or branch retinal vein occlusion. A total of 427 patients were randomised to OZURDEX and 426 to sham in the two Phase III studies. A total of 401 patients (94 %) randomised and treated with OZURDEX completed the initial treatment period (up to day 180).

A total of 47.3 % of patients experienced at least one adverse reaction. The most frequently reported adverse reactions in patients who received OZURDEX were increased intraocular pressure (24.0 %) and conjunctival haemorrhage (14.7 %).

The adverse reaction profile for BRVO patients was similar to that observed for CRVO patients although the overall incidence of adverse reactions was higher for the subgroup of patients with CRVO.

b) The following adverse reactions, considered related to OZURDEX treatment were reported during the two Phase III clinical trials.

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000) adverse reactions are presented according to MedDRA System organ class in Table 1. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Frequency	Adverse reaction
Nervous system disorders	uncommon	Headache
Eye disorders	very common	Intraocular pressure increased, conjunctival haemorrhage*
	common	Ocular hypertension, vitreous detachment, cataract, subcapsular cataract, vitreous haemorrhage*, visual disturbance, vitreous opacities* (including vitreous floaters), eye pain*, photopsia*, conjunctival oedema*, anterior chamber cell*, conjunctival hyperaemia*
	uncommon	Retinal tear*, anterior chamber flare*

* Adverse reactions considered to be related to the intravitreous injection procedure rather than the dexamethasone implant

c) Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. During the initial treatment period,

0.7 % (3/421) of the patients who received OZURDEX required laser or surgical procedures for management of elevated IOP in the study eye compared with 0.2 % (1/423) with sham.

The adverse reaction profile of 341 patients analysed following a second injection of OZURDEX, was similar to that following the first injection. A total of 54 % of patients experienced at least one adverse reaction. The incidence of increased IOP(24.9 %) was similar to that seen following the first injection and likewise returned to baseline by open-label day 180. The overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

4.9 Overdose

If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinflammatory agents, ATC code: S01BA01

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. Vascular Endothelial Growth Factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular oedema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

The efficacy of OZURDEX was assessed in two multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1,267 patients who received treatment with dexamethasone 350 µg or 700 µg implants or sham (studies 206207-008 and 206207-009). A total of 427 were randomised to OZURDEX, 414 to dexamethasone 350 µg and 426 patients to sham.

Based on the pooled analysis results, treatment with OZURDEX implants showed statistically significantly greater incidence of responders, defined as patients achieving a $\geq$ 15 letter improvement from baseline in Best Corrected Visual Acuity (BCVA) at 90 days following injection of a single implant, when compared with sham ($p < 0.001$).

The proportion of patients achieving the primary efficacy measure of $\geq$ 15 letter improvement from baseline in BCVA following injection of a single implant is shown in Table 2. A treatment effect was seen at the first observation time point of day 30. The maximum treatment effect was observed at day 60 and the difference in the incidence of responders was statistically significant favouring OZURDEX compared with sham at all time points to day 90 following injection. There continued to be a numerically greater proportion of responders for a $\geq$ 15 letter improvement from baseline in BCVA in patients treated with OZURDEX compared with sham at day 180.

Table 2. Proportion of Patients with ≥ 15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Pooled, ITT Population)

Visit	OZURDEX N = 427	Sham N = 426
Day 30	21.3 % [a]	7.5%
Day 60	29.3% [a]	11.3%
Day 90	21.8% [a]	13.1%
Day 180	21.5%	17.6%

[a] Proportion significantly higher with OZURDEX compared to sham ($p < 0.001$)

The mean change from baseline BCVA was significantly greater with OZURDEX compared to sham at all time points.

In each Phase III study and the pooled analysis, the time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response curves were significantly different with OZURDEX compared to sham ($p < 0.001$) with OZURDEX treated patients achieving a 3-line improvement in BCVA earlier than sham treated patients.

OZURDEX was numerically superior to sham in preventing vision loss as shown by a lower of proportion of patients experiencing deterioration of vision of ≥ 15 letters in the OZURDEX group throughout the 6-month assessment period

In each of the phase III studies and the pooled analysis, mean retinal thickness was significantly less, and the mean reduction from baseline was significantly greater, with OZURDEX (-207.9 microns) compared to sham (-95.0 microns) at day 90 ($p < 0.001$, pooled data). The treatment effect as assessed by BCVA at day 90 was thus supported by this anatomical finding. By Day 180 the mean retinal thickness reduction (-119.3 microns) compared with sham was not significant.

Patients who had a BCVA score of <84 OR retinal thickness > 250 microns by optical coherence tomography OCT and in the investigator's opinion treatment would not put the patient at risk; were eligible to receive an OZURDEX treatment in an open label extension. Of the patients who were treated in the open label phase, 93% received an OZURDEX injection between 5 and 7 months after the initial treatment.

As for the initial treatment, peak response was seen at Day 60 in the open label phase. The cumulative response rates were higher throughout the open label phase in those patients receiving two consecutive OZURDEX injections compared with those patients who had not received an OZURDEX injection in the initial phase.

The proportion of responders at each time point was always greater after the second treatment compared with the first treatment. Whereas, delaying treatment for 6 months results in a lower proportion of responders at all time points in the open label phase when compared with those receiving a second OZURDEX injection.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with OZURDEX in all subsets of the paediatric population for retinal vascular occlusion. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Plasma concentrations were obtained from a subset of 21 patients in the two, 6-month efficacy studies prior to dosing and on day 7, 30, 60, and 90 following the intravitreal implant containing 350 µg or 700 µg dexamethasone. Ninety-five percent of the plasma dexamethasone concentration values for the 350 µg dose group and 86% for the 700 µg dose group were below the lower limit of quantitation (0.05 ng/ml). The highest plasma concentration value of 0.094 ng/ml was observed in one subject from the 700 µg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In a 6-month monkey study following a single intravitreal injection of OZURDEX the dexamethasone vitreous humour C_{max} was 100 ng/ml at day 42 post-injection and 5.57 ng/ml at day 91. Dexamethasone remained detectable in the vitreous at 6 months post-injection. The rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humour > aqueous humour > plasma.

In an *in vitro* metabolism study, following the incubation of [14C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humour, and sclera tissues for 18 hours, no metabolites were observed. This is consistent with results from rabbit and monkey ocular metabolism studies.

Dexamethasone is ultimately metabolised to lipid and water soluble metabolites that can be excreted in bile and urine.

The OZURDEX matrix slowly degrades to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at doses considered sufficiently in excess of the maximum dose for human indicating little relevance to clinical use.

No mutagenicity, carcinogenicity, reproductive or developmental toxicity data are available for OZURDEX. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application.

Dexamethasone exposure to the healthy/untreated eye via contralateral diffusion has been observed in rabbits following delivery of the implant to the posterior segment of the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Ester terminated 50:50 poly D,L-lactide-co-glycolide.
- Acid terminated 50:50 poly D,L-lactide-co-glycolide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 pack contains:

1 sustained release sterile implantable rod shaped implant containing 700 micrograms of dexamethasone, located in the needle (stainless steel) of a disposable applicator.

The applicator consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab.

The applicator containing the implant is packaged in a sealed foil pouch containing desiccant.

6.6 Special precautions for disposal and other handling

OZURDEX is for single use only.
Each applicator can only be used for the treatment of a single eye.

If the seal of the foil pouch containing the applicator is damaged, do not use. Once the foil pouch is opened the applicator should be used immediately.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road,
Co. Mayo
Westport
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. Manufacturing authorisation holder responsible for batch release

B. Conditions of the marketing authorisation

A. Manufacturing authorisation holder responsible for batch release

Name and address of the manufacturer responsible for batch release

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport, Co Mayo
Ireland

B. Conditions of the marketing authorisation

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics).

- **Conditions or restrictions with regard to the safe and effective use of the medicinal product**

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, at launch, all physicians who are expected to prescribe/use Ozurdex are provided with a physician information pack containing the following:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information pack

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Aseptic techniques to minimise the risk of infection
- Use of antibiotics
- Techniques for the intravitreal injection
- Patient monitoring after IVT injection
- Key signs and symptoms of IVT injection related adverse events including increased intraocular pressure, glaucoma, ocular hypertension, cataract, traumatic cataract related to injection technique, vitreous detachment, vitreous haemorrhage, endophthalmitis, mechanical failure of device and implant misplacement
- Management of IVT injection related adverse events

The patient information pack should be provided in both the form of patient information booklet and an audio-CD that contain following key elements:

- Patient information leaflet
- How to prepare for Ozurdex treatment
- What are the steps following treatment with Ozurdex
- Key signs and symptoms of serious adverse events including increased intraocular pressure and ocular hypertension
- When to seek urgent attention from their health care provider

- **Other conditions**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version version 2.0 dated March 2010 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.0 dated May 2010 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities

Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached

At the request of the European Medicines Agency

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND POUCH EXTENDED LABEL

1. NAME OF THE MEDICINAL PRODUCT

OZURDEX 700 micrograms intravitreal implant in applicator
Dexamethasone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One implant contains 700 micrograms of dexamethasone

3. LIST OF EXCIPIENTS

- Contains
- Ester terminated 50:50 poly D,L-lactide-co-glycolide.
- Acid terminated 50:50 poly D,L-lactide-co-glycolide.

4. PHARMACEUTICAL FORM AND CONTENTS

One intravitreal implant in applicator.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.
Read the package leaflet before use.
Intravitreal use.
Do not use if foil pouch seal is damaged.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once pouch opened, use applicator immediately.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

APPLICATOR LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

OZURDEX 700 micrograms intravitreal implant in applicator
Dexamethasone
Intravitreal use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 implant.

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

OZURDEX 700 micrograms intravitreal implant in applicator
Dexamethasone

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT OZURDEX IS AND WHAT IT IS USED FOR

The active substance in OZURDEX is dexamethasone. Dexamethasone belongs to a group of medicines called corticosteroids.

OZURDEX is used to treat vision loss in adults caused by a blockage of veins in the eye. This blockage leads to a build up of fluid causing swelling in the area of the retina (the light-sensitive layer at the back of the eye) called the macula. The swelling may lead to damage to the macula which affects your central vision which is used for tasks like reading. OZURDEX works by reducing this swelling of the macular which helps to lessen or prevent more damage to the macula.

2. BEFORE YOU ARE GIVEN OZURDEX

You must not be given OZURDEX

- if you are allergic (hypersensitive) to dexamethasone or any of the other ingredients of OZURDEX (for a full list of ingredients, see section 6 “FURTHER INFORMATION”),
- if you have an infection of any kind in or around your eye (bacterial, viral or fungal),
- if you have glaucoma or high pressure inside your eye which is not controlled properly with the medicines you may be using.

Take special care with OZURDEX

- Before your OZURDEX injection tell your doctor if:You have had cataract surgery
- You are taking any medicines to thin the blood
- You have had a herpes simplex infection in your eye in the past (an ulcer on the eye that has been there a long time, or sores on the eye).

Please tell your doctor immediately if you develop symptoms such as the following after injection with OZURDEX:
- blurred or decreased vision,
- eye pain or increased discomfort,
- worsening eye redness,
- a feeling of spots in front of the eye (sometimes called ‘floaters’),
- increased sensitivity to light,
- any discharge from the eye,

In some patients the pressure in the eye may increase for a short period straight after the injection, or you may develop an eye infection.

Increase in pressure in the eye can also occur at any time following injection, this is something you may not notice so your doctor will monitor you regularly after treatment.

The injection of OZURDEX into both eyes at the same time has not been studied and is not recommended. Your doctor should not inject OZURDEX into both eyes at the same time.

Children and adolescent (below 18 years of age)
The use of OZURDEX in children and adolescents has not been studied and is therefore not recommended.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
There is no experience of using OZURDEX in pregnant women or during breast-feeding. OZURDEX should not be used during pregnancy or breast-feeding unless your doctor thinks it is clearly necessary. If you are pregnant or planning to become pregnant, or if you are breast-feeding, please discuss this with your doctor before OZURDEX treatment. Ask your doctor for advice before taking any medicine.

Driving and using machines
After OZURDEX treatment you may experience some reduced vision for a short time. If this happens, do not drive or use any tools or machines until your vision improves.

3. HOW OZURDEX IS USED

All OZURDEX injections will be given by an appropriately qualified eye doctor.

The usual dose is one implant to be given by injection into your eye. If the effect of this injection wears off and your doctor recommends it, another implant may then be injected into your eye.

Your doctor will ask you to use antibiotic eye drops regularly before and after each injection to prevent any eye infection. Please follow these instructions carefully.

On the day of the injection, your doctor may use antibiotic eye drops to prevent infection. Your doctor will also give you a local anaesthetic to reduce or prevent any pain you might have with the injection. You may hear a ‘click’ during the injection of OZURDEX; this is normal.

There are detailed instructions for your doctor on how to carry out the OZURDEX injection at the end of this leaflet.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, OZURDEX can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:

Very common	affects more than 1 user in 10

Common	affects 1 to 10 users in 100
Uncommon	affects 1 to 10 users in 1,000
rare	affects 1 to 10 users in 10,000
very rare	affects less than 1 user in 10,000
not known	frequency cannot be estimated from the available data

The following side effects may be seen with OZURDEX:

Very common: Increased pressure in the eye, bleeding on the surface of the eye*

Common: High pressure in the eye, detachment of the jelly inside the eye from the light-sensitive layer at the back of the eye (vitreous detachment), clouding of the lens (cataract), bleeding into the inside of the eye*, difficulties in seeing clearly, a feeling of spots in front of the eye (including 'floaters')*, eye pain*, seeing flashes of light*, swelling on the surface of the eye*, a feeling of looking through mist or fog*, redness of the eye*

Uncommon: Tear of the light-sensitive layer at the back of the eye (retinal tear)*, increased protein in the front of the eye due to inflammation*, headache

**Some of these side effects may be caused by the injection procedure and not the OZURDEX implant itself.*

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE OZURDEX

Keep out of the reach and sight of children.

Do not use OZURDEX after the expiry date which is stated on the carton and the pouch after EXP:. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What OZURDEX contains

- The active substance is dexamethasone.
- Each implant contains 700 micrograms of dexamethasone.
- The other ingredients are: Ester terminated 50:50 poly D,L-lactide-co-glycolide and Acid terminated 50:50 poly D,L-lactide-co-glycolide.

What OZURDEX looks like and contents of the pack

OZURDEX is a rod-shaped implant which is stored inside the needle of an applicator. The applicator and a packet of drying material are sealed in a foil pouch which is inside a carton. One carton contains one applicator with one implant which will be used once and thrown away.

Marketing Authorisation Holder and Manufacturer

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
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B-1560 Hoeilaart
Tél/Tel: +32 (0)2 351 2424
E-mail: uk_medinfo@allergan.com

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for medical or healthcare professionals only:

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

1. NAME OF THE MEDICINAL PRODUCT

OZURDEX 700 micrograms intravitreal implant in applicator

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One implant contains 700 micrograms of dexamethasone.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intravitreal implant in applicator.
Disposable injection device, containing a rod-shaped implant. which is not visible. The implant is approximately 0.46 mm in diameter and 6 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OZURDEX is indicated for the treatment of adult patients with macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO) (see section 5.1).

4.2 Posology and method of administration

OZURDEX must be administered by a qualified ophthalmologist experienced in intravitreal injections.

Posology
The recommended dose is one OZURDEX implant to be administered intra-vitreally to the affected eye. Administration to both eyes concurrently is not recommended (see section 4.4).

Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the physician's ~~investigator's~~ opinion may benefit from retreatment without being exposed ~~at~~ to significant risk. (see section 5.1)

Patients who experience and retain improved vision should not be retreated. Patients who experience a deterioration in vision, which is not slowed by OZURDEX, should not be retreated.

There is only very limited information on repeat dosing intervals less than 6 months (see section 5.1). There is currently no experience of repeat administrations beyond 2 implants in Retinal Vein Occlusion.

Patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs (see section 4.4).

Special populations
Elderly (≥65 years old)
No dose adjustment is required for elderly patients.

Renal impairment
OZURDEX has not been studied in patients with renal impairment however no special considerations are needed in this population.

Hepatic impairment
OZURDEX has not been studied in patients with hepatic impairment, however no special considerations are needed in this population.

Paediatric population
There is no relevant use of OZURDEX in the paediatric population in macular oedema following either Branch Retinal Vein Occlusion (BRVO) or Central Retinal Vein Occlusion (CRVO).

Method of administration
Single-use intravitreal implant in applicator for intravitreal use only.
Each applicator can only be used for the treatment of a single eye.

The intravitreal injection procedure should be carried out under controlled aseptic conditions which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent).

A broad spectrum topical antimicrobial should be given prior to and on the day of the injection procedure. Adequate local anaesthesia should be administered. Remove the foil pouch from the carton and examine for damage (see section 6.6). Then, in a sterile field, open the foil pouch and gently place the applicator on a sterile tray. Carefully remove the cap from the applicator. Once the foil pouch is opened the applicator should be used immediately.

Hold the applicator in one hand and pull the safety tab straight off the applicator. Do not twist or flex the tab. With the bevel of the needle up away from the sclera, advance the needle about 1 mm into the sclera then redirect toward the centre of the eye into the vitreous cavity until the silicone sleeve is against the conjunctiva. Slowly press the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully pressed and has locked flush with the applicator surface. Remove the needle in the same direction as used to enter the vitreous.

Immediately after injecting OZURDEX, use indirect ophthalmoscopy in the quadrant of injection to confirm successful implantation. Visualisation is possible in the large majority of cases. In cases in which the implant cannot be visualised, take a sterile cotton bud and lightly depress over the injection site to bring the implant into view.

Following the intravitreal injection patients should continue to be treated with a broad spectrum antimicrobial.

4.3 Contraindications

OZURDEX is contraindicated in

- Hypersensitivity to the active substance or to any of the excipients.
- Active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
- Advanced glaucoma which cannot be adequately controlled by medicinal products alone.

4.4 Special warnings and precautions for use

Monitoring
Any intravitreous injection can be associated with endophthalmitis, intraocular inflammation, increased intraocular pressure and retinal detachment. Proper aseptic injection techniques must always

be used. In addition, patients should be monitored following the injection to permit early treatment if an infection or increased intraocular pressure occurs. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy between two and seven days following the injection.

Patients must be instructed to report any symptoms suggestive of endophthalmitis or any of the above mentioned events without delay.

Adverse reactions
Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma and may result in secondary ocular infections.

In clinical studies,cataract was reported more frequently in patients with phakic lens receiving a second injection (see section 4.8with only 1 patient out of 368 requiring cataract surgery during the first treatment and 3 patients out of 302 during the second treatment.
As expected with ocular steroid treatment and intravitreal injections, increases in intraocular pressure (IOP) may be seen. Of the patients experiencing an increase of IOP of ≥10 mmHg from baseline, the greatest proportion showed this IOP increase at around 60 days following an injection. Patients of less than 45 years of age are more likely to experience increases in IOP. Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post-injection as needed.

Other warnings and precautions
Corticosteroids should be used cautiously in patients with a history of *ocular herpes simplex* and not be used in active *ocular herpes simplex*.

The safety and efficacy of OZURDEX administered to both eyes concurrently have not been studied. Therefore administration to both eyes concurrently is not recommended.

OZURDEX has not been studied in aphakic patients Therefore OZURDEX should be used with caution in these patients.

OZURDEX has not been studied in patients with macular oedema secondary to RVO with significant retinal ischemia. Therefore OZURDEX is not recommended.

Anti-coagulant therapy was used in 1.7% of patients receiving OZURDEX; there were no reports of hemorrhagic adverse events in these patients. Anti-platelet medicinal products, such as clopidogrel, were used at some stage during the clinical studies in over 40% of patients. In clinical trial patients receiving anti-platelet therapy, haemorrhagic adverse events were reported in a higher proportion of patients injected with OZURDEX (27%) compared with the control group (20%). The most common haemorrhagic adverse reaction reported was conjunctival haemorrhage (24%). OZURDEX should be used with caution in patients taking anti-coagulant or anti-platelet medicinal products.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Systemic absorption is minimal and no interactions are anticipated.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown teratogenic effects following topical ophthalmic administration (see section 5.3). There are no adequate data from the use of intravitreally administered dexamethasone in pregnant women. Long-term systemic treatment with glucocorticoids during pregnancy increases the risk for intra-uterine growth retardation and adrenal insufficiency of the newborn child. Therefore, although the systemic exposure of dexamethasone would be expected to be very low after local,

intraocular treatment. OZURDEX is not recommended during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Breast feeding
Dexamethasone is excreted in breast milk No effects on the child are anticipated due to the route of administration and the resulting systemic levels. However OZURDEX is not recommended during breast feeding unless clearly necessary.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive and use machines

Patients may experience temporarily reduced vision after receiving OZURDEX by intravitreal injection (see section 4.8). They should not drive or use machines until this has resolved.

4.8 Undesirable effects

a) The clinical safety of OZURDEX has been assessed in two Phase III randomised, double-masked, sham-controlled studies in patients with macular oedema following central retinal vein occlusion or branch retinal vein occlusion. A total of 427 patients were randomised to OZURDEX and 426 to sham in the two Phase III studies. A total of 401 patients (94 %) randomised and treated with OZURDEX completed the initial treatment period (up to day 180).

A total of 47.3 % of patients experienced at least one adverse reaction. The most frequently reported adverse reactions in patients who received OZURDEX were increased intraocular pressure (24.0 %) and conjunctival haemorrhage (14.7 %).

The adverse reaction profile for BRVO patients was similar to that observed for CRVO patients although the overall incidence of adverse reactions was higher for the subgroup of patients with CRVO.

b) The following adverse reactions, considered related to OZURDEX treatment were reported during the two Phase III clinical trials.

Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000) adverse reactions are presented according to MedDRA System organ class in Table 1. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Frequency	Adverse reaction
Nervous system disorders	uncommon	Headache
Eye disorders	very common	Intraocular pressure increased, conjunctival haemorrhage*
	common	Ocular hypertension, vitreous detachment, cataract, subcapsular cataract, vitreous haemorrhage*, visual disturbance, vitreous opacities* (including vitreous floaters), eye pain*, photopsia*, conjunctival oedema*, anterior chamber cell*, conjunctival hyperaemia*
	uncommon	Retinal tear*, anterior chamber flare*

* Adverse reactions considered to be related to the intravitreous injection procedure rather than the dexamethasone implant

c) Increased intraocular pressure (IOP) with OZURDEX peaked at day 60 and returned to baseline levels by day 180. Elevations of IOP either did not require treatment or were managed with the temporary use of topical IOP-lowering medicinal products. During the initial treatment period, 0.7 % (3/421) of the patients who received OZURDEX required laser or surgical procedures for management of elevated IOP in the study eye compared with 0.2 % (1/423) with sham.

The adverse reaction profile of 341 patients analysed following a second injection of OZURDEX, was similar to that following the first injection. A total of 54 % of patients experienced at least one adverse reaction. The incidence of increased IOP(24.9 %) was similar to that seen following the first injection and likewise returned to baseline by open-label day 180. The overall incidence of cataracts was higher after 1 year compared to the initial 6 months.

4.9 Overdose

If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, antiinflammatory agents, ATC code: S01BA01

Dexamethasone, a potent corticosteroid, has been shown to suppress inflammation by inhibiting oedema, fibrin deposition, capillary leakage, and phagocytic migration of the inflammatory response. Vascular Endothelial Growth Factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular oedema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular oedema.

The efficacy of OZURDEX was assessed in two multicentre, double-masked, randomised, sham-controlled, parallel studies of identical design which together comprised 1,267 patients who received treatment with dexamethasone 350 µg or 700 µg implants or sham (studies 206207-008 and 206207-009). A total of 427 were randomised to OZURDEX, 414 to dexamethasone 350 µg and 426 patients to sham.

Based on the pooled analysis results, treatment with OZURDEX implants showed statistically significantly greater incidence of responders, defined as patients achieving a $\geq$ 15 letter improvement from baseline in Best Corrected Visual Acuity (BCVA) at 90 days following injection of a single implant, when compared with sham ($p < 0.001$).

The proportion of patients achieving the primary efficacy measure of $\geq$ 15 letter improvement from baseline in BCVA following injection of a single implant is shown in Table 2. A treatment effect was seen at the first observation time point of day 30. The maximum treatment effect was observed at day 60 and the difference in the incidence of responders was statistically significant favouring OZURDEX compared with sham at all time points to day 90 following injection. There continued to be a numerically greater proportion of responders for a $\geq$ 15 letter improvement from baseline in BCVA in patients treated with OZURDEX compared with sham at day 180.

Table 2. Proportion of Patients with ≥ 15 Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Pooled, ITT Population)

Visit	OZURDEX N = 427	Sham N = 426
Day 30	21.3 % [a]	7.5%
Day 60	29.3% [a]	11.3%
Day 90	21.8% [a]	13.1%
Day 180	21.5%	17.6%

[a] Proportion significantly higher with OZURDEX compared to sham ($p < 0.001$)

The mean change from baseline BCVA was significantly greater with OZURDEX compared to sham at all time points.

In each Phase III study and the pooled analysis, the time to achieve ≥ 15 letters (3-line) improvement in BCVA cumulative response curves were significantly different with OZURDEX compared to sham ($p < 0.001$) with OZURDEX treated patients achieving a 3-line improvement in BCVA earlier than sham treated patients.

OZURDEX was numerically superior to sham in preventing vision loss as shown by a lower of proportion of patients experiencing deterioration of vision of ≥ 15 letters in the OZURDEX group throughout the 6-month assessment period

In each of the phase III studies and the pooled analysis, mean retinal thickness was significantly less, and the mean reduction from baseline was significantly greater, with OZURDEX (-207.9 microns) compared to sham (-95.0 microns) at day 90 ($p < 0.001$, pooled data). The treatment effect as assessed by BCVA at day 90 was thus supported by this anatomical finding. By Day 180 the mean retinal thickness reduction (-119.3 microns) compared with sham was not significant.

Patients who had a BCVA score of <84 OR retinal thickness > 250 microns by optical coherence tomography OCT and in the investigator's opinion treatment would not put the patient at risk; were eligible to receive an OZURDEX treatment in an open label extension. Of the patients who were treated in the open label phase, 93% received an OZURDEX injection between 5 and 7 months after the initial treatment.

As for the initial treatment, peak response was seen at Day 60 in the open label phase. The cumulative response rates were higher throughout the open label phase in those patients receiving two consecutive OZURDEX injections compared with those patients who had not received an OZURDEX injection in the initial phase.

The proportion of responders at each time point was always greater after the second treatment compared with the first treatment. Whereas, delaying treatment for 6 months results in a lower proportion of responders at all time points in the open label phase when compared with those receiving a second OZURDEX injection.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with OZURDEX in all subsets of the paediatric population for retinal vascular occlusion. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Plasma concentrations were obtained from a subset of 21 patients in the two, 6-month efficacy studies prior to dosing and on day 7, 30, 60, and 90 following the intravitreal implant containing 350 µg or 700 µg dexamethasone. Ninety-five percent of the plasma dexamethasone concentration values for the 350 µg dose group and 86% for the 700 µg dose group were below the lower limit of quantitation (0.05 ng/ml). The highest plasma concentration value of 0.094 ng/ml was observed in one subject from the 700 µg group. Plasma dexamethasone concentration did not appear to be related to age, body weight, or sex of patients.

In a 6-month monkey study following a single intravitreal injection of OZURDEX the dexamethasone vitreous humour C_{max} was 100 ng/ml at day 42 post-injection and 5.57 ng/ml at day 91. Dexamethasone remained detectable in the vitreous at 6 months post-injection. The rank order of dexamethasone concentration was retina > iris > ciliary body > vitreous humour > aqueous humour > plasma.

In an *in vitro* metabolism study, following the incubation of [14C]-dexamethasone with human cornea, iris-ciliary body, choroid, retina, vitreous humour, and sclera tissues for 18 hours, no metabolites were observed. This is consistent with results from rabbit and monkey ocular metabolism studies.

Dexamethasone is ultimately metabolised to lipid and water soluble metabolites that can be excreted in bile and urine.

The OZURDEX matrix slowly degrades to lactic acid and glycolic acid through simple hydrolysis, then further degrades into carbon dioxide and water.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at doses considered sufficiently in excess of the maximum dose for human indicating little relevance to clinical use.

No mutagenicity, carcinogenicity, reproductive or developmental toxicity data are available for OZURDEX. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application.

Dexamethasone exposure to the healthy/untreated eye via contralateral diffusion has been observed in rabbits following delivery of the implant to the posterior segment of the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Ester terminated 50:50 poly D,L-lactide-co-glycolide.
- Acid terminated 50:50 poly D,L-lactide-co-glycolide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 pack contains:

1 sustained release sterile implantable rod shaped implant containing 700 micrograms of dexamethasone, located in the needle (stainless steel) of a disposable applicator.

The applicator consists of a plunger (stainless steel) within a needle where the implant is held in place by a sleeve (silicone). The plunger is controlled by a lever on the side of the applicator body. The needle is protected by a cap and the lever by a safety tab.

The applicator containing the implant is packaged in a sealed foil pouch containing desiccant.

6.6 Special precautions for disposal and other handling

OZURDEX is for single use only.
Each applicator can only be used for the treatment of a single eye.

If the seal of the foil pouch containing the applicator is damaged, do not use. Once the foil pouch is opened the applicator should be used immediately.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.